It's All Greek To Me

By Richard Lathe; CNS Newsletter, Edinburgh 1998

Aristotle. I'm worried about Molecular Neuroscience, it doesn't seem to be going anywhere.

Plato. Now why is that? Surely everyone is working hard and progress is being made?

Aristotle. I suppose so. Analysis of the dopaminergic system has certainly given some new insights and therapies. Yes, some genes responsible for important neurological disorders have been identified. But I do worry that too much work is on the tedious detail of the ultrastructure of some esoteric subcellular specialisation or phenomenon, like the sequence of the transmembrane domain of a receptor for a neuronal growth factor only expressed in the subiculum of south american bats.

Plato. But what's wrong with that? Surely this work is of intrinsic value?

Aristotle. Please don't get me wrong, I'm certainly not detracting from such lines of approach. My worry is that the pursuit of such systems might not be justifiable when the Neuroscientists don't have answers to even the simplest and most fundamental questions.

Plato. Such as?

Aristotle. You put me on the spot there. Um, how about - does long term potentiation (LTP) have anything whatsoever to do with memory? Is amyloid deposition a cause or a consequence of Alzheimer's disease? Or even, do excitatory neurones transmit information through their firing rate alone or do they cluster their discharges into bursts?

Plato. Surely the modern biotechnological approaches are making inroads?

Aristotle. Quite right, but there are some difficulties. Let me give you an example. Protein Z is suspected of being intimately involved in synaptic plasticity, because drugs that block this protein block LTP in the hippocampal slices. So the protein Z gene is altered, and homozygous mice are produced, and what happens? Well, that's a long story. Either LTP is altered, or it is not, or only in some animals. The mice either learn to navigate in the swim maze, or they do not, or most do but some don't. Or, worse, they are sometimes fine in one type of navigation test but impaired in another. So a qualitative modification, like the disruption of a gene, usually produces only a quantitative change in some parameter chosen by the experimenter.

Plato. I see, that is indeed very worrying. But I would have thought that such problems of interpretation are encountered across all the biosciences.

Aristotle. Not quite. Let's look at an example from oncology. A developing tumour has a clonal origin, can be cultured in vitro, and when reintroduced into an appropriate host gives rise to a new tumour. Gene sequencing reveals that the tumour contains a mutationally activated oncogene - clone this gene out, put it back into a cell line or a transgenic animal and, hey presto, a new tumour! The system is well-adapted for analysis.

Plato. So what's different about Molecular Neuroscience?

Aristotle. The first problem is that the Molecular Neuroscientist is still unable to isolate a simple neuronal circuit with which to tinker, free of extraneous influences. Now this kind of problem is encountered in many fields of biology - in endocrinology for instance.

Changes in adrenal steroid production cause changes in blood pressure that in turn cause changes to the kidney and the heart. To understand this system, however, the experimenter can modify steroid hormone levels or action, can alter blood pressure by

other means, and the hormone effects can be dissociated into fast and slow effects. So it's not too bad.

It's quite different in the brain. If drugs are introduced into one brain region, what happens? Well, they start acting on adjacent brain regions that probably deal with a different kind of information processing. And, worse, the target brain region is in constant communication with other brain regions that, of course, respond to the changes introduced. So if tinkering with one brain nucleus causes changes in a particular behaviour, it's really pretty difficult to draw any meaningful conclusions!

Plato. That I am beginning to see. Is that the only problem?

Aristotle. I wish it was. The second problem is that individual behaviours cannot be isolated. Any task presented to the animal, or even the patient, draws on a composite of multiple interacting brain circuits, every one modulating what the animal does at any point in time. So how can the outcome of any intervention be interpreted?

Plato. I am beginning to feel most unwell. What do you advise?

Aristotle. I really wish I knew. But maybe it should be turned around. Why not try to guess what particular brain regions might do, how their circuitry might contribute to information processing, and what kind of processing, how the neurones making up those circuits might actually talk to each other, in other words, how the brain might *really* work - and only then reach for the micropipette and the electrode to see how the theory holds up.

Plato. As simple as that? I think not. But an interesting idea, I will reflect upon it.